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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.
09/603,658	06/23/00	ZHU	L 25636-703

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EXAMINER	
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ART UNIT	**PAPER NUMBER**
1627	5

DATE MAILED: 03/20/01

Please find below and/or attached an Office communication concerning this application or proceeding.

Commissioner of Patents and Trademarks

Office Action Summary	Application No.	Applicant(s)	
	09/603,658	ZHU ET AL.	
	Examiner	Art Unit	
	Thomas W Prasthofer	1627	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136 (a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *25 September 2000* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-38* is/are pending in the application.

4a) Of the above claim(s) *24-34* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-27 and 35-38* is/are rejected.

7)☒ Claim(s) *25 and 35* is/are objected to.

8)☐ Claims _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are objected to by the Examiner.

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. § 119

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. & 119(e).

Attachment(s)

15) ☒ Notice of References Cited (PTO-892)
16) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
17) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
18) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
19) ☐ Notice of Informal Patent Application (PTO-152)
20) ☐ Other: .

Detailed Action

Status of the Application

Receipt is acknowledged of a preliminary amendment on 09/25/00 (Paper No. 4).

Status of the Claims

Claims 1-38 are pending in the present application. During a telephone conversation with Dr. Shirley Chen on February 7, 2001 a provisional election was made without traverse to prosecute the invention of Group I, claims 1-27 and 35-38. Affirmation of this election must be made by applicant in replying to this Office action. Claims 28-34 are withdrawn from further consideration by the examiner, 37 CFR 1.142(b), as being drawn to a non-elected invention. Claims 1-27 and 35-38 are being examined on their merits.

Election/Restriction

1. Restriction to one of the following inventions is required under 35 U.S.C. 121:

   I. Claims 1-27 and 35-38, drawn to a library of yeast expression vectors encoding a library of fusion proteins and a library of transformed yeast cells comprising yeast cells transformed with a library of yeast expression vectors, classified in class 435, subclass 255.1.

   II. Claims 28-34, drawn to a library of expression vectors, classified in class 435, subclass 320.1.

The inventions are distinct, each from the other because:

2. Inventions I and II are different and patentably distinct compositions. Invention I is comprises a library of yeast expression vectors and yeast cells transformed with yeast expression vectors while Invention II comprises a library of expression vectors and may include bacterial, mammalian, and viral vectors as well as yeast expression vectors. The expression vectors of Inventions I and II require different functional components, operate in different types of cells in different environments, and produce different post-translational products. Art anticipating or rendering obvious Invention I would not anticipate or render obvious Invention II. Each invention would support separate patents.

3. Because these inventions are distinct for the reasons given above and

a. have acquired a separate status in the art as shown by their different classification ;

b. have different and separately burdensome: manual and/or computer: structure, name and bibliographical searches; and

c. have divergent subject matter, restriction for examination purposes as indicated is proper.

4. Applicant is advised that the reply to this requirement to be complete must include an election of the invention to be examined even though the requirement be traversed (37 CFR 1.143).

5. Applicant is reminded that upon the cancellation of claims to a non-elected invention, the inventorship must be amended in compliance with 37 CFR 1.48(b) if one or more of the currently named inventors is no longer an inventor of at least one claim remaining in the application. Any amendment of inventorship must be accompanied by a diligently filed petition under 37 CFR 1.48(b) and by the fee required under CFR 1.17(h).

Objections to the Claims

6. Claim 25 is objected to because no SEQ I.D. NO. is given for the amino acid sequence.

7. Claim 35 is objected to because it appears that the word "with" is missing from the claim. The claim recites "A library of transformed yeast cells, comprising: yeast cells transformed [ ] a library of yeast expression vectors..."

Claims Rejections - 35 U.S.C. 101

35 U.S.C. 101 reads as follows:

> Whoever invents or discovers any new and useful process, machine, manufacture, or composition of matter, or any new and useful improvement thereof, may obtain a patent therefor, subject to the conditions and requirements of this title.

8. Claims 1-27 and 35-38 are rejected under 35 U.S.C. 101 because the claimed invention is not supported by either a specific and/or substantial asserted utility or a well established utility.

The instant specification discloses that the claimed library can be used for "screening against target molecules such as proteins, peptides, DNAs, and small molecules in vitro and in vivo" (abstract, lines 17-20).

Applicant's claimed library of yeast expression vectors and transformed yeast cells must satisfy 35 USC 101 and 112 (1) as defined by the statute and case law. In this regard, Applicant is directed to MPEP 2107; 2107.01 and 210.02 which provide guidelines for determining the criteria for satisfying utility and enablement.

Initially it is noted that merely disclosing the ability to make a compound or compounds (e.g. a library) is in itself insufficient utility to satisfy either 35 USC 101 or 112, first paragraph as determined by the U.S. Supreme Court. . Eg. See *Brenner v. Manson,* 383 U.S. 519, 148 USPQ 689 (1966).

According to the text of 35 USC sec. 101, an invention must be "useful". Our reviewing courts have applied the labels, "specific utility" (or "practical utility") to refer to this aspect of the "useful invention" requirement of sec. 101. (Nelson v. Bowler, 626 F.2d 853, 206 USPQ 881, 883 (CCPA 1980)). In Nelson, the court characterized "specific utility" (or "practical utility") as "a shorthand way of attributing real-world value to claimed subject matter. In other words, one skilled in the art can use a claimed discovery in a manner which provides some immediate benefit to the public." (Id. at 856.)

With respect to the issue of pharmaceutical utility and vague assertions of biological activity applicant is further directed to *In re Kirk* , 376 F.2d 936, 941, 153 USPQ 48, 52 (CCPA 1967)) and *Cross v. Iizuka* , 753 F.2d 1040, 224 USPQ 739 (Fed. Cir. 1985), wherein the Federal Circuit labeled applicant's assertion of "biological activity" without more specifics as a "nebulous" expression. Such statements, the court held, "convey little explicit indication regarding the utility of a compound" and do not satisfy either the utility and/or the enablement statutory requirements.

The claimed library of yeast expression vectors encoding a library of fusion proteins and library of transformed yeast cells, is not supported by a specific asserted utility and does not, without further research and experimentation, provide an immediate benefit to the public.

Rather, the claimed libraries must be screened against proteins, peptides, DNAs, or small molecules in vitro or in vivo. Since the library may express any combination of any possible fusion proteins and can be screened against essentially unlimited numbers of molecules, it is certain that some interactions between target molecules and the expressed fusion proteins could be found. This does not provide an immediate benefit to the public, however, because the disclosure does not provide adequate means or guidance for what libraries to generate, what molecules to screen them against, how to screen, or what utility any interactions identified may have. Any benefit to the public (to one of ordinary skill in the art) is speculative.

Thus, the determination of utility is to take place at some future time, only when the components of the library, test and/or target proteins molecules, and binding interactions have been elucidated. Absent a disclosure of those components and interactions, the asserted utility of "screening against target molecules such as proteins, peptides, DNAs, and small molecules in vitro and in vivo" lacks specificity. Note, because the claimed invention is not supported by a specific asserted utility for the reasons just set forth, credibility cannot be assessed.

This is not to say that inventions that are to be used exclusively in a research setting (i.e., research tools) always lack a specific asserted utility. Indeed, many research tools such as telescopes, gas chromatographs, screening assays, and nucleotide sequencing techniques have a clear, specific and unquestionable utility. (See USPTO Utility Guidelines, page 12.)

However, inventions that have a specifically identified utility must be distinguished from those whose utility requires further research to identify or reasonably confirm. (Id.) Research

tools (such as gas chromatographs, screening assays, etc.) are useful in the sense that they can be used in conjunction with other method steps to evaluate materials other than themselves or to arrive at some result.

In the absence of an asserted specific utility, the "useful" requirement may be established by reference to a well established utility. A "well established utility" is a "specific utility" which is well known, immediately apparent and implied by the specification based on the disclosure of the properties of a material, alone or taken with the knowledge of one skilled in the art.

The libraries claimed are not supported by a well established utility, however, because neither the specification as filed nor any art of record discloses or suggests any property or activity for the target molecules to be identified such that another non-asserted utility would be well established for these combinations of molecules.

Claims Rejections - 35 U.S.C. 112, 1st Paragraph

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

9. Claims 1-27 and 35-38 are also rejected under 35 U.S.C. 112, first paragraph. Specifically, since the claimed invention is not supported by either a specific and/or substantial asserted utility or a well established utility for the reasons set forth above, one skilled in the art clearly would not know how to use the claimed invention.

10. Claims 1-15, 20-27, and 35-38 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

With respect to adequate disclosure of the scope of the presently claimed generic Applicant is referred to the discussion in *University of California v. Eli Lilly and Co.* U.S. Court

of Appeals Federal Circuit (CA FC) 43 USPQ2d 1398 7/22/1997 Decided July 22, 1997 No. 96-1175 regarding disclosure. Adequate disclosure, like enablement, requires *representative examples* which provide reasonable assurance to one skilled in the art that the compounds falling within the scope, both possess the alleged utility and additionally demonstrate that *applicant had possession of the full scope of the claimed invention*. See In re Riat et al. (CCPA 1964) 327 F2d 685, 140 USPQ 471; In re Barr et al. (CCPA 1971) 444 F 2d 349, 151 USPQ 724 (for enablement) and *University of California v. Eli Lilly and Co* cited above (for disclosure). The more unpredictable the art the greater the showing required (e.g. by "representative examples") for both enablement and adequate disclosure.

Unlike *Lilly*, applicant does not have a single example of a yeast expression library within the scope of the presently claimed invention and thus does not provide even a single expression library species in support of a potentially broad generic of different and nonexemplified libraries (e.g. substitute C-DNA in Lilly with yeast expression libraries) which generic is much broader than the Lilly generic invention.

Like Lilly, applicant asserts that there is a means of obtaining these peptides; however, this is not relevant to the disclosure requirement in which the applicant must demonstrate possession of the claimed scope at the time of filing.

Claims Rejections - 35 U.S.C. 112, 2nd Paragraph

The following is a quotation of the second paragraph of 35 U.S.C. 112:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

11. Claim 10 is rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. The claim recites that the precursor sequences "are not specifically designed for a target peptide or protein." Is the phrase intended to exclude fusion proteins in which either of the two subunits are known to bind to a particular peptide or protein that is to be used as a target or any peptide or protein even if it is not to be used as a target? Are fusion proteins composed of subunits known to or specifically designed to bind to small molecules excluded? Are naturally

occurring proteins or subunits known to bind a particular peptide or protein considered to be "specifically designed" for a peptide or protein?

12. Claims 11 and 12 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. The claims recite that polypeptide subunits are not derived or generated from one or more proteins "that are known to bind to a target peptide or protein." Does this mean that any polypeptide subunit derived or generated from a protein that is known to bind to any target peptide or protein, specifically or non-specifically, is to be excluded from the library even if that target is not to be used in screening?

13. Claim 11 is rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. The term "derived from" is vague and indefinite because the neither the claims nor the specification provide a definition of or a means of determining whether a polypeptide sequence is "derived from" another. Through mutagenesis one might generate any number of sequences that may include portions of sequence homology with other proteins.

14. Claim 12 is rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. The term "generated by mutagenizing one or more proteins" is vague and indefinite because the neither the claims nor the specification provide a definition of or a means of determining whether a polypeptide sequence is "generated by mutagenizing one or more proteins." Through mutagenesis (including, for example, deletion or insertions of 50% or more of a sequence) one might generate sequences that may include portions of sequence homology with other proteins. There are no metes and bounds provided for one using the invention to determine the limitations of the term "generated by mutagenizing one or more proteins."

15. Claim 13 is rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. Claim 13 recites that the first and second polypeptide subunits are "subunits of a multimeric protein whose sequence varies within a library of multimeric proteins." It is not clear how the sequence of a single multimeric protein can vary within a library of a plurality of multimeric proteins.

165. Claim 20 is rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. The term "substantially conserved conformation" in claim 15 is a relative term which renders the claim indefinite. The term " substantially conserved conformation" is not defined by the claim, the specification does not provide a standard for ascertaining the requisite degree, and one of ordinary skill in the art would not be reasonably apprised of the scope of the invention. The relative conformations between the first and second polypeptide subunits have been rendered indefinite.

17. Claim 21 is rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. The term "mimics" in claim 21 is a relative term which renders the claim indefinite. The term "mimics" is not defined by the claim, the specification does not provide a standard for ascertaining the requisite degree, and one of ordinary skill in the art would not be reasonably apprised of the scope of the invention. In the context of the claim, "mimics" is used to indicate similarity in function or structure. One structure mimics another similar structure to a degree but, without further qualification, the degree of structural similarity between molecules in order to say that one structure "mimics" the other is a matter of judgement and not definite.

Claims Rejections - 35 U.S.C. 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless –

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

18. Claims 1-21, 25-27, and 35-38 are rejected under 35 U.S.C. 102(b) as being anticipated by Hoeffler et al. (1999, WO 99/28502).

The Hoeffler et al. reference teaches libraries of yeast expression vectors encoding libraries of single chain antibodies comprising a first nucleotide sequence encoding either V_H or V_L subunit, a second nucleotide sequence encoding either V_L or V_H subunit, and a peptide linker that connects the two subunits (see, for example, page 5, lines 1-16, page 7, lines 10-13, and figure 4). The yeast expression vectors include the yeast 2μ and bacterial origins of replication and are yeast-bacteria shuttle vectors (figure 4). The single chain antibody libraries are comprehensive populations of V_L and V_H subunits (vary independently from one another) linked by short, flexible peptide linkers (page 8, lines 16-17). The reference presents an invention that can probe an animal's entire repertoire of $> 10^{12}$ combinations of light and heavy variable chains (page 11, lines 12-15, 21-22, and 25). The yeast strains used can be diploid or haploid and may be mated (page 22, lines 21-24). The use of $\underline{\alpha}$ and $\underline{a}$ strains of haploid yeast for mating is the most common method of yeast mating. The preferred linker in the Hoeffler et al. reference if a $[(Gly)_4Ser]_3$ peptide (page 24, line 27). The source of DNA for generating the single chain antibody expression vectors may be from immunized or non-immunized animals including humans and mice and from tissues including spleen cells and lymphoblastoid cells (page 32, lines 5-10). The immunoglobulin variable regions can be amplified without prior knowledge of their sequences (or binding properties) (page 33, lines 5-6) and the fusions can be tagged with poly-Histidine for purification (page 43, lines 24-25).

19. Claims 1-3, 15-17, 19-24, 26, 35, and 36 are rejected under 35 U.S.C. 102(b) as being anticipated by Filupa et al. (1998) WO 98/49198.

The Filupa et al. reference teaches a number of different single chain antibody (SCA) fusion protein yeast expression vectors and yeast transformed with these vectors. The vectors comprise nucleotides encoding V_L and V_H subunits connected by linker sequences (page 2, lines

9-12, page 8, lines 6-11, and page 9, lines 12-20). The source of the nucleotides can be human or mouse (figures 7 and 8) and the V_L and V_H subunits may encoded in either order from 5' to 3' (page 19, lines 9-27). The preferred peptide linker should be from 2 to about 50 or 18 to about 30 residues (page 21, lines 23-24 and page 22, lines 17-18). At east 18 different expression vectors are taught that comprise sequences in the two subunits that vary independently of one another (page 29, line13 – page 30, line 22, page 67, lines 15-17, and page 76, claim 1.). The reference teaches that other proteins may also be modified including cell adhesion proteins, IgA, IgG, IgD, IgE, IgM, enzymes, cytokines, and growth factors (page 30, line 26 - page 31, line 14). The yeast expression vector includes the yeast 2μ circle (page 35, line 4) and is transformed into yeast (page 36, lines 8-10).

Claims Rejections - 35 U.S.C. 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

20. Claims 1-27, and 35-38 are rejected under 35 U.S.C. 103(a) as being unpatentable over Hoeffler et al. (1999), WO 99/28502 and Filupa et al. (1998) WO 98/49198.

The Hoeffler et al. reference teaches yeast expression vectors comprising two-subunit fusion proteins in which heavy-chain and light chain variable are joined by a linker sequence and the sequence of each subunit varies independently within the library. The reference also teaches yeast expression vectors that are bacterial shuttle vectors, library diversity greater than 10^{12}, human and rodent sources of coding sequences, spleen and peripheral blood cell sources of coding sequences, GGGGS tandem repeat linker sequences, affinity tagged single chain antibodies including poly-Histidine, haploid and diploid yeast cells transformed with the expression vectors, and mating of haploid transformed yeast.

Hoeffler et al. do not explicitly teach linker sequences that are 30-120, 45-102, or 45-63 bp in length.

The Filupa et al. reference teaches the use of linkers in single chain antibodies that are 2-50 and 18-30 bp in length. It would have been obvious to one of ordinary skill in the art at the time that the invention was made to use the linkers of Filupa et al. with the expression libraries of Hoeffler et al. According to Filupa et al. page 22, lines 15-19, "linkers having 18-30 residues are most preferred for SCA (single chain antibody) polypeptides in the monovalent conformation." Similarly, the same reference states "The preferred length of the peptide linker should be from 2 to about 50 amino acids. In each particular case, the preferred length will depend upon the nature of the polypeptides to be linked and the desired activity..." One would have had reasonable expectation for success because linkers as disclosed in the references had already been used successfully.

21. Any inquiry concerning this communication or earlier communications from the examiner should be directed to **Thomas W. Prasthofer** whose telephone number is **(703) 308-4548**. The examiner can normally be reached on Monday-Friday, 8:00-4:30.

22. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Jyothsna Venkat can be reached on (703) 308-2439. The fax phone number for the organization where this application or proceeding is assigned is (703) 308-2742.

23. Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (703) 308-1235.

Thomas Prasthofer, Ph.D.
3/15/01

BENNETT CELSA
PRIMARY EXAMINER

3/16/01